

Green solvents for sustainable organic synthesis: state of the art†

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The growing awareness of the pressing need for greener, more sustainable technologies has focused attention on the use of atom efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. Another aspect which is receiving increasing attention is the use of alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents. The use of nonconventional reaction media also provides opportunities for facilitating the recovery and recycling of the catalyst. The state of the art in the use of alternative reaction media for green, sustainable organic synthesis is reviewed. Liquid–liquid biphasic catalysis provides an industrially attractive method for the recovery and recycling of catalysts as an alternative to the more traditional solid heterogeneous catalysts. Various approaches to liquid–liquid biphasic catalysis—aqueous biphasic, fluorous biphasic, supercritical carbon dioxide, ionic liquids and various combinations thereof—are reviewed and compared. “The best solvent is no solvent” but if a solvent is needed then water has a lot to recommend it and catalysis in aqueous biphasic systems is an industrially attractive methodology which has found broad application. Similarly, supercritical carbon dioxide is an interesting reaction medium in the context of green chemistry and catalysis in various mono- and biphasic systems involving this solvent are reviewed. Fluorous biphasic systems and ionic liquids also have advantages in certain situations and the advantages and limitations of these media are compared. The ultimate in clean catalytic technologies is to telescope multistep syntheses into one-pot in the form of catalytic cascade processes. Examples of such catalytic cascades involving both chemo- and biocatalytic conversions are presented. Biocatalysis has a distinct advantage in this context in that the reactions all take place at or close to ambient temperature and pressure. In emulation of natural processes, where several different enzymes are compartmentalised in the cell, it can be advantageous to immobilise the various catalysts in such a cascade process. In this context, a novel and effective method for the immobilisation of enzymes as cross-linked enzyme aggregates (CLEAs) is discussed and the use of a combi CLEA, containing two enzymes, for the one-pot conversion of benzaldehyde to *S*-mandelic acid is reported.

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Roger Sheldon (1942) received a PhD in organic chemistry from the University of Leicester (UK) in 1967. This was followed by post-doctoral studies with Prof. Jay Kochi in the US. From 1969 to 1980 he was with Shell Research in Amsterdam and from 1980 to 1990 he was R&D Director of DSM Andeno. In 1991 he moved to his present position as Professor of Biocatalysis and Organic Chemistry at the Delft University of Technology (The Netherlands). His primary research interests are in the application of catalytic methodologies—homogeneous, heterogeneous and enzymatic—in organic synthesis, particularly in relation to fine chemicals production. He developed the concept of E factors for assessing the environmental impact of chemical processes.

Introduction

It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry. This trend towards what has become known as ‘Green Chemistry’ or ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

A reasonable working definition of green chemistry can be formulated as follows: *green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

A useful measure of the potential environmental acceptability of chemical processes is the E factor,¹ defined as the mass ratio of waste to desired product. The sheer magnitude of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 1). The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids

Table 1 E Factors in the chemical industry

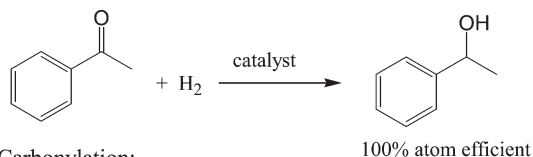
	Tonnage	E = kg waste/kg product
Bulk chemicals	10^4 – 10^6	<1–5
Fine chemical industry	10^2 – 10^4	5–>50
Pharmaceutical industry	10 – 10^3	25–>100

and, in principle, even fuel (although this is often difficult to quantify). There is one exception: (process) water is generally not taken into account.

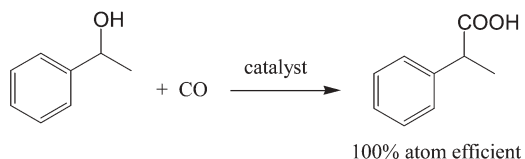
The waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture is rampant with antiquated 'stoichiometric' technologies. Examples, which readily come to mind are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents (LiAlH_4 , NaBH_4), oxidations with permanganate, manganese dioxide and chromium(VI) reagents and a wide variety of reactions, *e.g.* sulfonations, nitrations, halogenations, diazotisations and Friedel–Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4 , HF, H_3PO_4) and Lewis acids (AlCl_3 , ZnCl_2 , BF_3).

The solution is evident: substitution of classical stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2 , O_2 , H_2O_2 , CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, carbonylation, hydroformylation and oxidation are good examples of highly atom efficient, low-salt processes (Fig. 1).

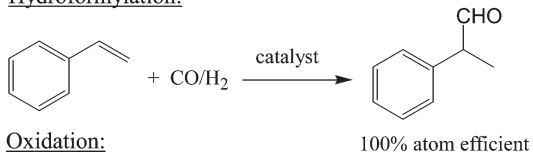
Hydrogenation:



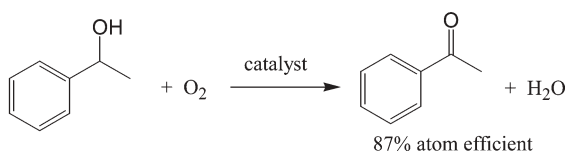
Carbonylation:



Hydroformylation:



Oxidation:

**Fig. 1** Atom efficient processes.

It is also worth noting in this context that there is currently much emphasis on the use of renewable raw materials (biomass) as a future source of energy, polymers and bulk and fine chemicals.² The biomass is derived from carbon dioxide and water, with the aid of solar energy, *via* photosynthesis. Hence, the basic raw materials of the future will be carbon dioxide, water, oxygen and nitrogen, with conversion of biomass in biorefineries replacing the conversion of fossil fuels in conventional oil refineries.

The question of solvents: alternative reaction media

Another important issue in green chemistry is the use of organic solvents. It has been estimated by GlaxoSmithKline workers³ that *ca.* 85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents, and recovery efficiencies are typically 50–80%. In the redesign of the sertraline manufacturing process,⁴ for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002, among other improvements a three step sequence was streamlined to a single step employing ethanol as the sole solvent. This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene and hexane) employed in the original process.

In the context of green chemistry there are several issues which influence the choice of solvent. It should be relatively nontoxic and relatively nonhazardous, *e.g.* not inflammable or corrosive. The solvent should also be contained, that is it should not be released to the environment. Solvent use is being subjected to close scrutiny and increasingly stringent environmental legislation and the FDA has issued guidelines which can be found on their website (<http://www.fda.gov/cder/guidance/index.htm>).

Removal of residual solvent from products is usually achieved by evaporation or distillation and most popular solvents are, therefore, highly volatile. Spillage and evaporation inevitably leads to atmospheric pollution, a major environmental issue of global proportions. Moreover, worker exposure to volatile organic compounds (VOCs) is a serious health issue. Many chlorinated hydrocarbon solvents have already been banned or are likely to be in the near future. Unfortunately, many of these solvents are exactly those that have otherwise desirable properties and are, therefore, widely popular for performing organic reactions. Another class of solvents which presents environmental problems comprises the polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, that are the solvents of choice for, *e.g.* many nucleophilic substitutions. They are high boiling and not easily removed by distillation. They are also water-miscible which enables their separation by washing with water. Unfortunately, this inevitably leads to contaminated aqueous effluent.

These issues surrounding a wide range of volatile and nonvolatile, polar aprotic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. There is a marked trend away from hydrocarbons and chlorinated hydrocarbons towards lower alcohols, esters and, in some cases, ethers. Inexpensive natural products such as ethanol have the added advantage of being readily

biodegradable and ethyl lactate, produced by combining two innocuous natural products, is currently being touted as an environmentally attractive solvent for chemical reactions.

In this context it is worth mentioning that poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) have attracted interest as novel solvents for catalytic processes. They are both relatively inexpensive and readily available materials. They are essentially nontoxic (PPG finds use as a solvent for pharmaceutical and cosmetic preparations and both PPG and PEG are approved for use in beverages) and biodegradable. Furthermore, they are, depending on the molecular weight, immiscible with water, nonvolatile, thermally robust, and can in principle be recycled after removal of the product. Hence, combinations of PEG or PPG with, *e.g.* water or scCO_2 are of interest as media for biphasic catalysis (see later).

PEG-200 and/or PEG-400 (the number refers to the average molecular weight), for example, have been used for the polyoxometalate catalysed aerobic oxidation of benzylic alcohols,⁵ the Wacker oxidation of propylene to acetone⁵ and Heck reactions.⁶

Alternative reaction media and multiphasic catalysis

The conclusion is clear: the problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and reuse. Alternative solvents should, therefore, provide for their efficient removal from the product and reuse.

The subject of alternative reaction media also touches on another issue: recovery and reuse of the catalyst. This is desirable from both an environmental and an economic viewpoint (many of the catalysts used in fine chemicals manufacture contain highly expensive noble metals and/or chiral ligands). If a catalyst is an insoluble solid, that is, a heterogeneous catalyst, it can easily be separated by centrifugation or filtration. In contrast, if it is a homogeneous catalyst, dissolved in the reaction medium, this presents more of a problem and offsets the major advantages of homogeneous catalysts, such as high activities and selectivities (see Table 2). A serious shortcoming of homogeneous catalysis is the cumbersome separation of the (expensive) catalyst from reaction products and the quantitative recovery of the catalyst in an active form. Separation by distillation of reaction products from the catalyst generally leads to heavy ends which remain in the catalyst phase and eventually deactivate it. In the manufacture of pharmaceuticals quantitative separation of the catalyst is important in order to avoid contamination of the product. Consequently there have been many attempts

to heterogenise homogeneous catalysts by attachment to organic or inorganic supports. However, these approaches have, generally speaking, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.

This need for efficient separation of product and catalyst, while maintaining the advantages of a homogeneous catalyst, has led to the concept of liquid–liquid biphasic catalysis, whereby the catalyst is dissolved in one phase and the reactants and product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation. Obviously, both solvents are subject to the same restrictions as discussed above for monophasic systems. Several different combinations have been intensely studied in recent years, including *water (aqueous biphasic)*, *supercritical CO_2* , *fluorous biphasic*, and *ionic liquids*. It is worth noting that the use of water and supercritical carbon dioxide as reaction media is consistent with the above mentioned trend towards the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

Aqueous biphasic catalysis

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is nontoxic, non-flammable, abundantly available and inexpensive. Moreover, owing to its highly polar character one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely the cumbersome recovery and recycling of the catalyst. Thus, performing the reaction in an aqueous biphasic system, whereby the catalyst resides in the water phase and the product is dissolved in the organic phase,⁷ allows for recovery and recycling of the catalyst by simple phase separation.

An example of a large scale application of this concept is the Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propylene to *n*-butanal (Fig. 2), which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst.⁸

Pioneering studies of aqueous biphasic catalysis with water soluble organometallic complexes were performed by Joo and coworkers, in hydrogenation⁹ and Kuntz, in hydroformylation.¹⁰ Kuntz, for example, synthesised the water soluble ligand, tppts, and showed that its rhodium complex catalysed

Table 2 Heterogeneous vs. homogeneous catalysis

	Homogeneous	Heterogeneous
Advantages	<ul style="list-style-type: none"> - Mild reaction conditions - High activity and selectivity - Efficient heat transfer 	<ul style="list-style-type: none"> - Facile separation of catalyst and products - Continuous processing
Disadvantages	<ul style="list-style-type: none"> - Cumbersome separation and recycling of catalyst - Product contamination - Not readily adapted to continuous processing 	<ul style="list-style-type: none"> - Heat transfer problems - Low activity and selectivity

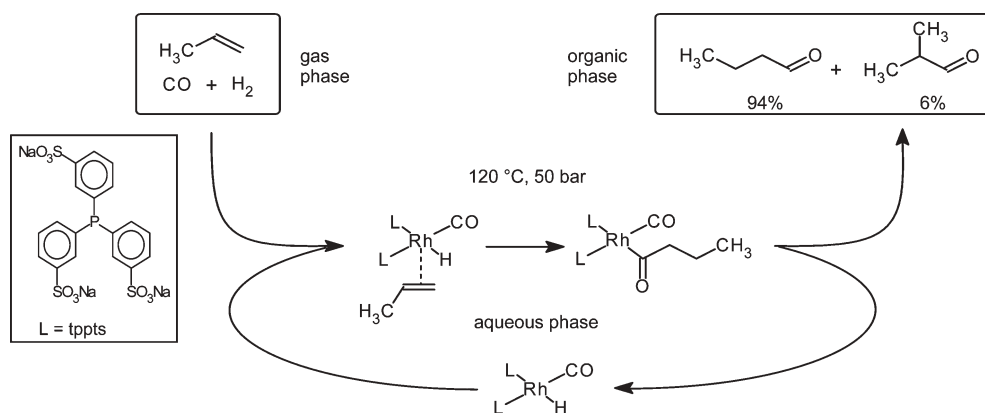


Fig. 2 Rhône-Poulenc/Ruhrchemie process for aqueous biphasic hydroformylation.

hydroformylations in water, thus laying the foundations for the Rhône-Poulenc/Ruhrchemie process for aqueous biphasic hydroformylation mentioned above.

Two decades later, we were interested in palladium catalysed carbonylations in water, with a view to carbonylating carbohydrates as renewable raw materials.¹¹ To this end, we synthesised the palladium(0) equivalent of the above mentioned rhodium–tppts complex¹² by allowing an aqueous solution of PdCl₂ and tppts (4 equiv.) to stand at room temperature for eight days. This resulted in the formation of Pd(tppts)₃ together with one equivalent of the corresponding phosphine oxide. Labelling experiments showed that the oxygen was derived from a water molecule (Fig. 3). In contrast, when the solution of PdCl₂ and tppts was subjected to 2 bar CO pressure, at room temperature, the Pd(tppts)₃ complex was formed in quantitative yield in 5 minutes. Hence, the carbonylation catalyst is rapidly formed, *in situ*, by mixing the ligand and a Pd(II) salt with CO in an aqueous medium.

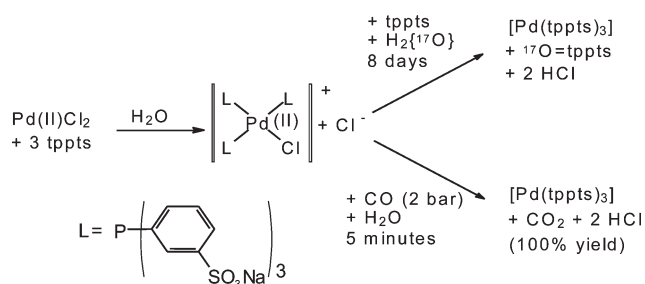


Fig. 3 Reaction of PdCl₂ with tppts in water.

The Pd(tppts)₃ complex was shown to catalyse the carbonylation of hydroxymethyl furfural (a model, carbohydrate-like substrate) in the presence of a Brønsted acid cocatalyst (Fig. 4). We subsequently showed that the same system catalysed the carbonylation of benzyl alcohol to phenylacetic acid (Fig. 4) in quantitative selectivity.¹³ The same methodology was also applied to the synthesis of ibuprofen by aqueous biphasic carbonylation of 1-(4-isobutylphenyl)ethanol (Fig. 4).¹⁴ The reaction is proposed to involve the formation of an intermediate carbenium ion (hence the need for an acid cocatalyst) which reacts with the Pd(0) complex to afford an alkyl-palladium(II) species.¹⁵

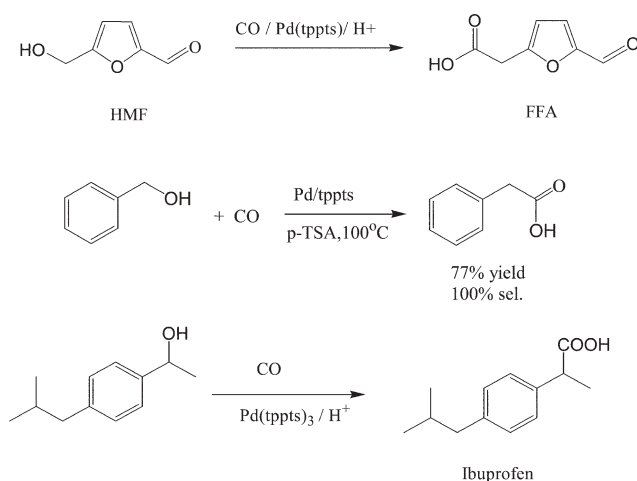
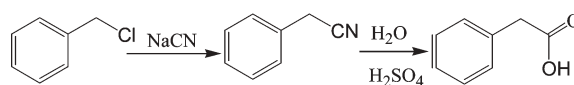


Fig. 4 Alcohol carbonylation in an aqueous biphasic system.

Similarly, Pd–tppts was used by Kohlpaintner and Beller (Hoechst)¹⁶ as the catalyst in the synthesis of phenylacetic acid by biphasic carbonylation of benzyl chloride as an alternative to the classical synthesis *via* reaction with sodium cyanide (Fig. 5). Although the new process still produces one equivalent of sodium chloride, this is substantially less salt generation than in the original process. Moreover, sodium cyanide is about seven times more expensive per kg than carbon monoxide.

Existing process:



New process:

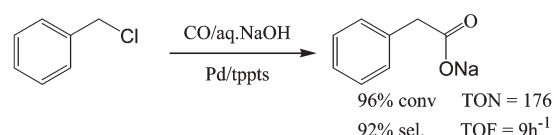


Fig. 5 Aqueous biphasic carbonylation.

We,¹⁷ and others¹⁸ subsequently showed that the same system, Pd–tppts, catalyses the aqueous biphasic hydrocarboxylation of olefins. When a sulfonated diphosphine is used as the

ligand the complex formed with palladium(0) catalyses the alternating copolymerisation of ethylene and CO to give the engineering thermoplastic polyketone, Carilon.^{19,20} Indeed, when a well-defined complex was used exceptionally high activities were observed,²⁰ with turnover frequencies (TOFs) higher than the conventional catalyst in methanol as solvent.

Oxidations

The palladium(II) complex of sulfonated bathophenanthroline was used in a highly effective aqueous biphasic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes or carboxylic acids and ketones respectively (Fig. 6).²¹ No organic solvent was necessary, unless the substrate is a solid, and turnover frequencies of the order of 100 h⁻¹ were observed. The catalyst could be recovered and recycled by simple phase separation (the aqueous phase is the bottom layer and can be left in the reactor for the next batch). The method constitutes an excellent example of a green catalytic oxidation with oxygen (air) as the oxidant, no organic solvent and a stable recyclable catalyst. The only disadvantage of the use of water as a solvent for aerobic oxidations is the low solubility of oxygen in water. Combined with the necessity (for safety reasons) of diluting the oxygen with nitrogen, this means that a pressure of 10–30 bar is needed to provide a sufficient concentration of oxygen in the aqueous phase.

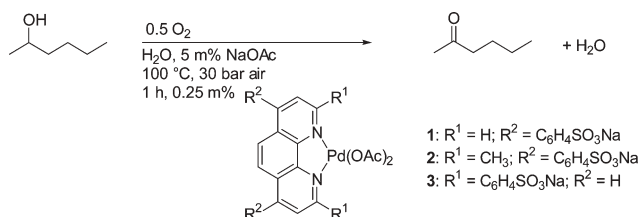


Fig. 6 Aqueous biphasic Pd catalysed aerobic oxidation of alcohols.

Alternatively, the use of hydrogen peroxide as the terminal oxidant is eminently compatible with the use of water as the reaction medium and hydrogen peroxide has been used, in aqueous biphasic systems, for the oxidation of alcohols to aldehydes or ketones, the epoxidation of olefins and the oxidative cleavage of olefins or ketones to carboxylic acids, *e.g.* cyclohexene to adipic acid (Fig. 7).²²

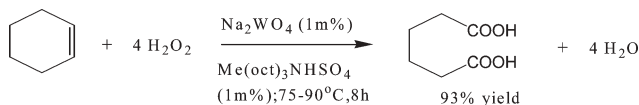


Fig. 7 Green synthesis of adipic acid.

Biocatalysis

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible catalyst (an enzyme) and solvent (often water) combined with high activities and chemo-, regio- and stereoselectivities in multi-functional molecules. Furthermore, the use of enzymes

generally circumvents the need for functional group activation and avoids the protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less waste and are, therefore, both environmentally and economically more attractive than conventional routes.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis and according to a recent estimate²³ more than 130 processes have been commercialised. Advances in recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price. Advances in protein engineering have made it possible, using techniques such as site directed mutagenesis and *in vitro* evolution, to manipulate enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, *etc.*²⁴ Furthermore, the development of effective immobilisation techniques has paved the way for optimising the performance and recovery and recycling of enzymes.

An illustrative example of the benefits to be gained by replacing conventional chemistry by biocatalysis is provided by the manufacture of 6-aminopenicillanic acid (6-APA), a key raw material for semi-synthetic penicillin and cephalosporin antibiotics, by hydrolysis of penicillin G.²⁵ Up until the mid-1980s a chemical procedure was used for this hydrolysis (Fig. 8). It involved the use of environmentally unattractive reagents, a chlorinated hydrocarbon solvent (CH₂Cl₂) and a reaction temperature of –40 °C. Thus, 0.6 kg Me₃SiCl, 1.2 kg PCl₅, 1.6 kg PhNMe₂, 0.2 kg NH₃, 8.4 l of *n*-BuOH and 8.4 l of CH₂Cl₂ were required to produce 1 kg of 6-APA. In contrast, enzymatic cleavage of penicillin G is performed in water at 37 °C and the only reagent used is NH₃ (0.09 kg per kg of 6-APA), to adjust the pH. The enzymatic process currently accounts for the majority of the several thousand tons of 6-APA produced annually on a world-wide basis.

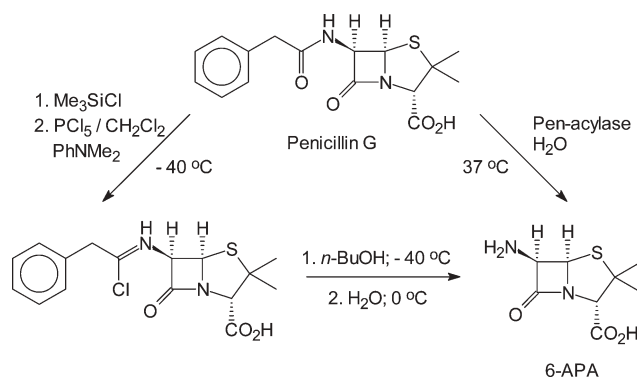


Fig. 8 Enzymatic versus chemical deacylation of penicillin G.

Another advantage of biocatalysis is the high degree of chemo-, regio- and stereoselectivities which are difficult or impossible to achieve by chemical means. A pertinent example is the production of the artificial sweetener, aspartame. The enzymatic process, operated by the Holland Sweetener Company (a joint venture of DSM and Tosoh) is completely regio- and enantiospecific (Fig. 9).²⁶

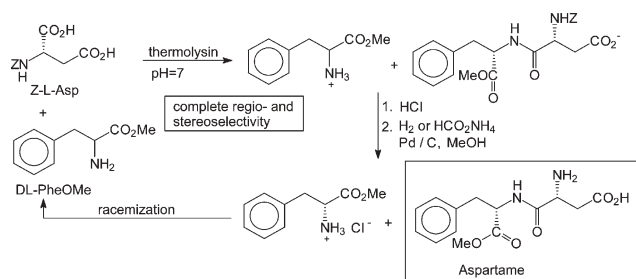


Fig. 9 Enzymatic synthesis of aspartame.

DuPont has developed a process for the manufacture of glyoxylic acid, a large volume fine chemical, by aerobic oxidation of glycolic acid (Fig. 10), mediated by resting whole cells of a recombinant methylotrophic yeast.²⁷ The glycolic acid is readily available from acid-catalysed carbonylation of formaldehyde. Traditionally, glyoxylic acid was produced by nitric acid oxidation of acetaldehyde or glyoxal, processes with high E factors. The key enzyme in the biocatalytic process is an oxidase which utilises dioxygen as the oxidant, producing one equivalent of hydrogen peroxide, without the need for cofactor regeneration.

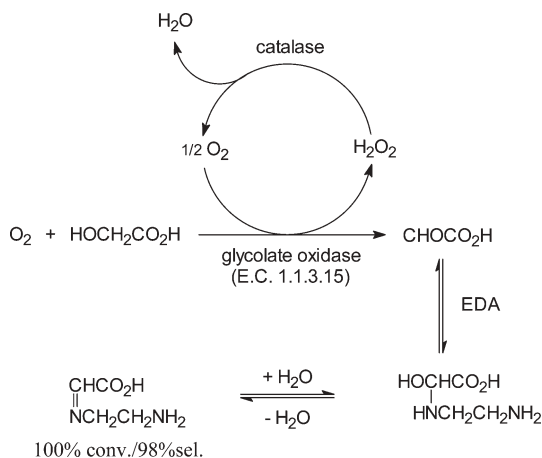


Fig. 10 Biocatalytic production of glyoxylic acid using whole cells of recombinant *Pichia pastoris*; pH 8.9–9.5/8 bar O₂/5 °C/2 h.

Another class of enzymes which catalyse the oxidation of alcohols comprises the alcohol dehydrogenases. However, in this case cofactor regeneration is required, which is an impediment to commercialisation. Recently, a highly enantioselective alcohol dehydrogenase, showing broad substrate specificity and exceptionally high tolerance for organic solvents, was isolated from *Rhodococcus ruber* DSM 4451.²⁸ The enzyme maintains a high activity at concentrations of up to 20% (v/v) acetone and 50% (v/v) 2-propanol. This enables the use of the enzyme, conveniently as whole microbial cells, as a catalyst for (enantioselective) Oppenauer oxidation of a broad range of alcohols, using acetone (20% v/v in phosphate buffer at pH 8) as the oxidant (Fig. 11), with substrate concentrations up to 1.8 mol l⁻¹ (237 g l⁻¹ for octan-2-ol). Alternatively, the reaction could be performed in a reduction mode, using a prochiral ketone as substrate and up to 50% v/v

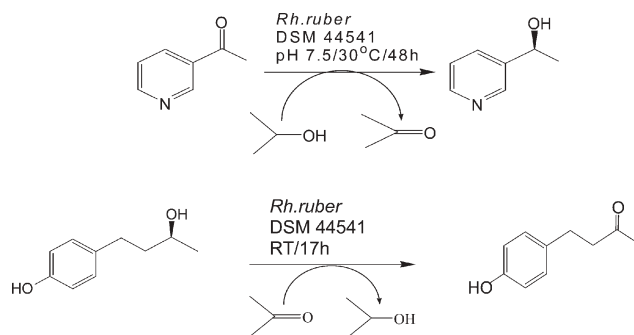


Fig. 11 Biocatalytic Oppenauer oxidations and Meerwein Ponndorf Verley reductions.

isopropanol as the reductant, affording the corresponding (*S*)-alcohol in 99% ee at conversions ranging from 65–92%.

Supercritical carbon dioxide as a reaction medium

Other nonclassical reaction media have, in recent years, attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and recycling.²⁹ For example, supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years.³⁰ Several features of scCO₂ make it an interesting solvent in the context of green chemistry and catalysis. For carbon dioxide the critical pressure and temperature are moderate: 74 bar and 31 °C, respectively. Hence, the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is nontoxic, chemically inert towards many substances, nonflammable, and simple depressurisation results in its removal. It is miscible with, *e.g.* hydrogen, making it an interesting solvent for hydrogenation and hydroformylation (see below). Furthermore, the physical properties of scCO₂, *e.g.* polarity, can be tuned by manipulation of the temperature and pressure. Although it is a greenhouse gas its use involves no net addition to the atmosphere; it is borrowed as it were. Its main uses are as a replacement for VOCs in extraction processes. For example it is widely used for the decaffeination of coffee where it replaced the use of a chlorinated hydrocarbon. The pre-existence of an established SCF extraction industry meant that the necessary equipment was already available.

Hydrogenation and hydroformylation

The use of scCO₂ as a solvent for catalytic hydrogenation was pioneered by Poliakoff and has been commercialised by Thomas Swan and Co. for the manufacture of trimethyl cyclohexanone by Pd catalysed hydrogenation of isophorone (Fig. 12).³¹ The miscibility of scCO₂ with hydrogen results in high diffusion rates, and provides the basis for achieving much

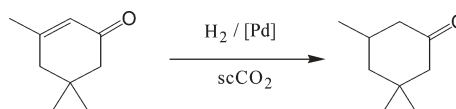


Fig. 12 Hydrogenation of isophorone in scCO₂.

higher reaction rates than in conventional solvents. The high reaction rates allow for the use of exceptionally small flow reactors. Chemoselectivities with multifunctional compounds could be adjusted by minor variations in reaction parameters. Similarly, scCO_2 has been used for olefin hydroformylation using an immobilised rhodium catalyst.³²

Oxidations

Just as with water, scCO_2 is also an ideal inert solvent for performing catalytic aerobic oxidations; it is nonflammable and completely miscible with oxygen. Recently, much interest has also been focused on catalytic oxidations with hydrogen peroxide, generated *in situ* by Pd-catalysed reaction of hydrogen with oxygen, in scCO_2 -water mixtures.³³ The system was used effectively for the direct epoxidation of propylene to propylene oxide over a Pd/TS-1 catalyst.³⁴ These reactions probably involve the intermediate formation of peroxycarboxylic acid by reaction of H_2O_2 with CO_2 (Fig. 13).

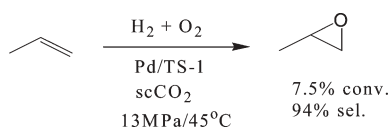


Fig. 13 Epoxidation of propylene with H_2 - O_2 in scCO_2 .

Biocatalysis

scCO_2 is also an interesting solvent for performing bioconversions. The first reports of biocatalysis in scCO_2 date back to 1985³⁵ and in the intervening two decades the subject has been extensively studied.³⁶ Enzymes are generally more stable in scCO_2 than in water and the *Candida antarctica* lipase (Novozym 435)-catalysed resolution of 1-phenylethanol was successfully performed at temperatures exceeding 100 °C in this solvent.³⁷ Matsuda *et al.* found that the enantioselectivity of alcohol acylations catalysed by Novozyme 435 in scCO_2 could be controlled by adjusting the pressure and temperature.³⁸ The same group recently reported a continuous flow system in scCO_2 for the enzymatic resolution of chiral secondary alcohols *via* Novozyme 435 catalysed acylation with vinyl acetate (Fig. 14).³⁹ For example, the kinetic resolution of 1-phenyl ethanol at 9 MPa CO_2 and 40 °C afforded the (*R*)-acetate in 99.8% ee and the (*S*)-alcohol in 90.6% ee at 48% conversion ($E = 1800$).

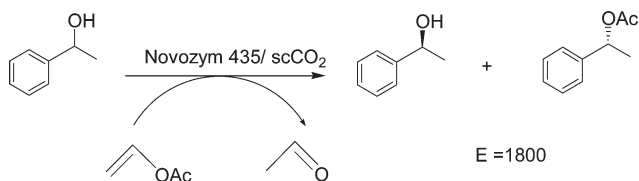


Fig. 14 Kinetic resolution of secondary alcohols with Novozyme 435 in scCO_2 .

Similarly, the enantioselective reduction of prochiral ketones catalysed by whole cells of *Geotrichum candidum* proceeded smoothly in scCO_2 in a semi-continuous flow system (Fig. 15).⁴⁰

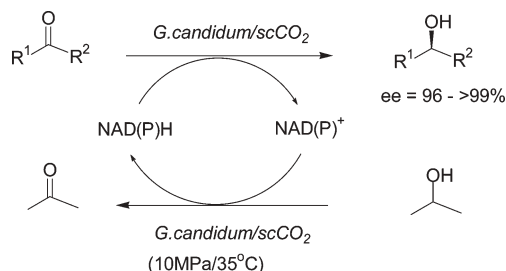


Fig. 15 Enantioselective reduction of prochiral ketones with immobilised resting cells of *Geotrichum candidum* in scCO_2 .

Enzyme catalysed oxidations with O_2 have also been successfully performed in scCO_2 *e.g.* using cholesterol oxidase⁴¹ and polyphenol oxidase.^{35b} The use of scCO_2 as a solvent for biotransformations clearly has considerable potential and we expect that it will find more applications in the future.

Fluorous biphasic systems

Fluorous biphasic catalysis was pioneered by Horváth and Rabai⁴² who coined the term ‘fluorous’ by analogy with ‘aqueous’, to describe highly fluorinated alkanes, ethers and tertiary amines. Such fluorinated compounds differ markedly from the corresponding hydrocarbon molecules and are, consequently, immiscible with many common organic solvents at ambient temperature although they can become miscible at elevated temperatures. Hence, this provides a basis for performing biphasic catalysis or, alternatively, monophasic catalysis at elevated temperatures with biphasic product-catalyst separation at lower temperatures.⁴³ A variety of fluorinated solvents are commercially available (see Fig. 16 for examples), albeit rather expensive compared with common organic solvents (or water).

In order to perform fluorous biphasic catalysis the (organometallic) catalyst needs to be solubilised in the fluorous phase by deploying ‘fluorophilic’ ligands, analogous to the hydrophilic ligands used in aqueous biphasic catalysis. This is accomplished by incorporating so-called ‘fluorous ponytails’.

Hydroformylation of higher olefins in an aqueous biphasic system is problematic owing to the lack of solubility of the substrate in the aqueous phase. On the other hand, hydroformylation in an organic medium presents the problem of separating the long-chain aldehydes from the catalyst. In contrast, this is not a problem with a fluorous biphasic system where at the elevated reaction temperature the mixture becomes a single phase. Cooling the reaction mixture to room temperature results in a separation into a fluorous phase, containing the catalyst, and an organic phase, containing the

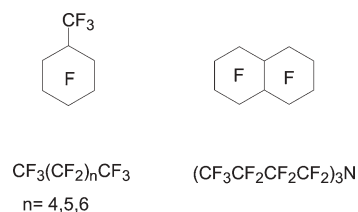


Fig. 16 Examples of fluorous solvents.

aldehyde products. This concept was applied by Horvath and Rabai, to the hydroformylation of 1-decene in a 1 : 1 mixture of $C_6F_{11}CF_3$ and toluene.⁴² The catalyst was prepared *in situ* from $Rh(CO)_2(acac)$ and $P[CH_2CH_2(CF_2)_5CF_3]_3$, (P/Rh = 40). Upon completion of the reaction the reactor was cooled to room temperature and phase separation occurred. When the upper, organic phase was returned to the reactor, with fresh reactants, negligible reaction was observed, demonstrating that catalytically active rhodium species are not leached into the organic phase. It was subsequently shown^{44,45} that recycling of the catalyst phase, in nine consecutive runs, afforded a total turnover number (TON) of more than 35 000. The rhodium losses amounted to 4.2%, which constitutes *ca.* 1 ppm per mole of aldehyde. Unfortunately there was some leaching of the free ligand into the organic phase, resulting in a slight decrease in (*n* : *iso*) selectivity (from *ca.* 92 : 8 to 89 : 11), which is dependent on the ligand–Rh ratio. The three different concepts for olefin hydroformylation—organic solvent, aqueous biphasic and fluororous biphasic—are compared in Fig. 17.

The successful demonstration of the fluororous biphasic concept for performing organometallic catalysis sparked extensive interest in the methodology and it has subsequently been applied to a wide variety of catalytic reactions.⁴³ Fluororous solvents are particularly suitable for performing aerobic oxidations based on the high solubility of oxygen in fluorocarbons. A few examples of catalytic oxidations in fluororous media have been reported. For example, the aerobic oxidation of alcohols was performed in a fluororous medium, using a copper complex with perfluorinated ligands.⁴⁶ Catalytic oxidations with hydrogen peroxide have also been performed in fluororous media.⁴⁷

Notwithstanding the seemingly enormous potential of the fluororous biphasic catalysis concept, as yet a commercial application has not been forthcoming. Presumably the cost of the solvents and ligands is a significant hurdle. Furthermore, although the catalyst and products are well-partitioned over the two phases, there is a finite solubility of the catalyst in the organic phase which has to be coped with.

Perhaps an even more serious problem is the extremely long lifetime of fluorocarbons in the environment which, even though they are chemically inert, essentially nontoxic and are not, in contrast to their cousins the CFCs, ozone-depleting agents, is still a matter for genuine concern.

In this context it is interesting to note the recent reports of *fluororous catalysis without fluororous solvents*.⁴⁸ The thermomorphous fluororous phosphines, $P[(CH_2)_m(CF_2)_7CF_3]_3$ (*m* = 2 or 3) exhibit *ca.* 600 fold increases in *n*-octane solubility between –20 and 80 °C. They catalyse the addition of alcohols to methyl propiolate in a monophasic system at 65 °C and can be recovered by precipitation on cooling. Similarly, we found that a perfluorinated ketone could be used as a catalyst for olefin epoxidations with hydrogen peroxide in organic solvents and subsequently recovered by cooling the reaction mixture to precipitate the ketone.⁴⁹

Ionic liquids

Ionic liquids are quite simply liquids that are composed entirely of ions.⁵⁰ They are generally salts of organic cations, *e.g.* tetraalkylammonium, alkylpyridinium, 1,3-dialkylimidazolium, tetraalkylphosphonium (Fig. 18). Room temperature ionic liquids exhibit certain properties which make them attractive media for performing green catalytic reactions. They have essentially no vapour pressure and are thermally robust with liquid ranges of *e.g.*, 300 °C, compared to 100 °C for water. Polarity and hydrophilicity/hydrophobicity can be tuned by a suitable combination of cation and anion, which has earned them the accolade, ‘designer solvents’.

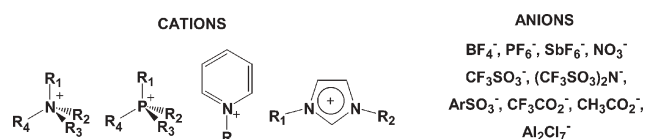


Fig. 18 Examples of ionic liquids.

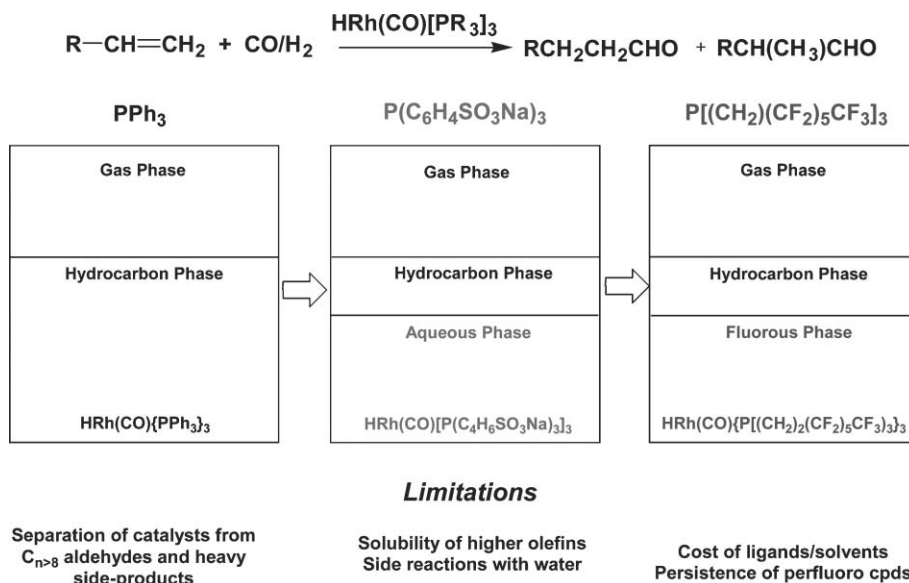
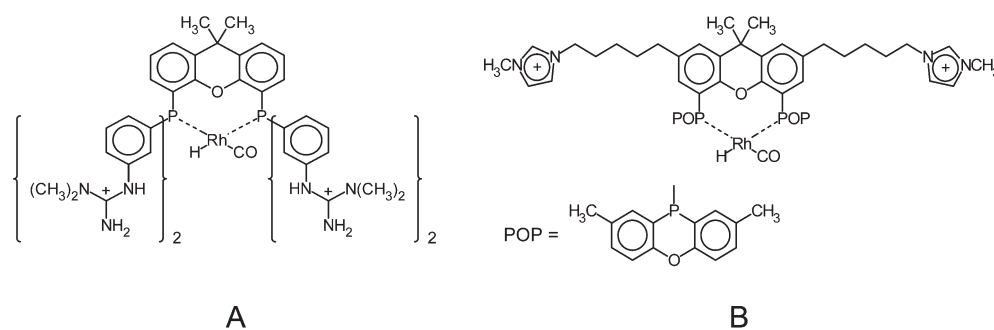


Fig. 17 Different concepts for olefin hydroformylation.



Catalyst	TOF(h ⁻¹)	n/iso ratio
(tppts) ₂ (CO)RhH	80	2.6
A	50	20
B	320	49

Fig. 19 Hydroformylation of 1-octene in [bmim][PF₆] at 100 °C and 30 bar.

Ionic liquids have been extensively studied in the last few years as media for organic synthesis and catalysis in particular.⁵¹ For example, the hydroformylation of higher olefins, such as 1-octene, was performed in ionic liquids.⁵² Good activities were observed with rhodium in combination with the water-soluble ligand, tppts, described above but the selectivity was low (n/iso ratio = 2.6). In order to achieve both high activities and selectivities special ligands had to be designed (Fig. 19). No detectable (less than 0.07%) Rh leaching was observed and the IL phase containing the catalyst could be recycled after separating the product which formed a separate phase. However, the need for rather exotic ligands will presumably translate to higher costs for this process compared to aqueous biphasic hydroformylation, for example.

In the last few years increasing attention has been devoted to conducting biocatalytic transformations in ionic liquids.⁵³ The first report of enzyme (lipase) catalysed reactions in water-free ionic liquids dates from 2000 and involved transesterification, ammoniolysis and perhydrolysis reactions catalysed by *Candida antarctica* lipase B, usually in its immobilised form, Novozyme 435 (Fig. 20).⁵⁴

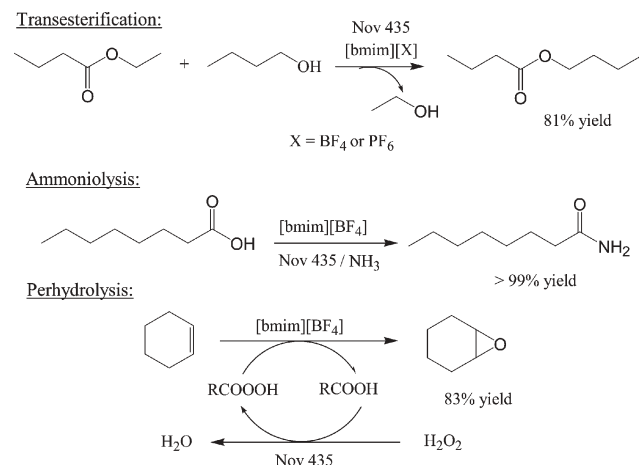


Fig. 20 *Candida antarctica* lipase B (Nov435) catalysed transformations in water-free ionic liquids.⁵⁴

The use of ionic liquids as reaction media for biotransformations has several potential benefits compared to conventional organic solvents, *e.g.*, higher operational stabilities and enantioselectivities⁵³ and activities are generally at least as high as those observed in organic solvents. They are particularly attractive for performing bioconversions with substrates which are very sparingly soluble in conventional organic solvents, *e.g.*, carbohydrates⁵⁵ and nucleosides.

Notwithstanding the advantages of ionic liquids as reaction media for catalytic processes, they have yet to be widely applied in industry. The reasons for this are probably related to their high prices and the paucity of data with regard to their toxicity and biodegradability. The replacement of conventional VOCs with ionic liquids is an obvious improvement with regard to atmospheric emissions but small amounts of ionic liquids will inevitably end up in the environment, *e.g.*, in ground water. Consequently, it is important to establish their effect on the environment. Indeed, the current trend in ionic liquid research is towards the development of nontoxic, biodegradable ionic liquids, *e.g.* based on renewable raw materials.⁵⁶

Biphasic systems with supercritical carbon dioxide

One problem associated with the use of ILs is recovery of the product and recycling of the catalyst. If this is achieved by extraction with a volatile organic solvent then it is questionable what the overall gain is. An attractive alternative is to use scCO₂ as the second phase, whereby the catalyst remains in the IL phase and the product is extracted into the scCO₂ phase. This concept has been successfully applied to both homogeneous metal catalysis⁵⁷ and biocatalytic conversions.⁵⁸ We have recently applied the concept of using a 'miscibility switch' for performing catalytic reactions in IL–scCO₂ mixtures.⁵⁹

Other combinations with scCO₂ have also been considered which dispense with the need for an ionic liquid altogether. For example, a biphasic water–scCO₂ system, whereby the catalyst, *e.g.* a metal complex of tppts, resides in the water phase and the product is removed in the scCO₂ phase.³⁰ The

system has its limitations: the catalyst needs to be water soluble and all reaction components must be stable towards the acidic pH (3) of carbonic acid. More recently, an attractive system comprising a biphasic mixture of poly(ethylene glycol) (PEG) to dissolve the catalyst and scCO_2 as the extractive phase was used for the $\text{RhCl}(\text{Ph}_3\text{P})_3$ -catalysed hydrogenation of styrene.⁶⁰ PEGs have the advantage over ILs that they are much less expensive and are nontoxic (analogous to CO_2 , they are approved for use in foods and beverages). They are, moreover, miscible with common organic ligands and in the above example the catalyst was stable and recyclable in the PEG phase.

Thermoregulated biphasic catalysis

Another approach to facilitating catalyst separation while maintaining the benefits of homogeneous catalysis involves the use of thermoregulated biphasic catalysis,⁶¹ whereby the catalyst is dissolved in a particular solvent at one temperature and insoluble at another. For example, a diphosphine ligand attached to an ethylene oxide–propylene oxide block copolymer (Fig. 21) afforded rhodium complexes that are soluble in water at room temperature but precipitate on warming to 40 °C. The driving force for this inverted temperature dependence on solubility is dehydration of the ligand on heating. Hence, a rhodium catalysed reaction, such as hydrogenation or hydroformylation can be performed at room temperature in a single phase and the catalyst separated by precipitation at a higher temperature. An added advantage is that runaway conditions are never achieved since the catalyst precipitates and the reaction stops on raising the temperature. This principle has also been applied to biotransformations by attaching enzymes to EO–PO block copolymers.⁶²

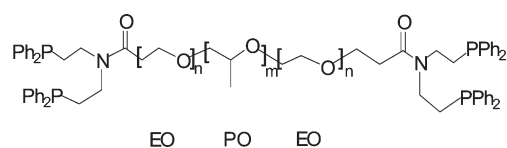


Fig. 21 Ligand for thermoregulated biphasic catalysis.

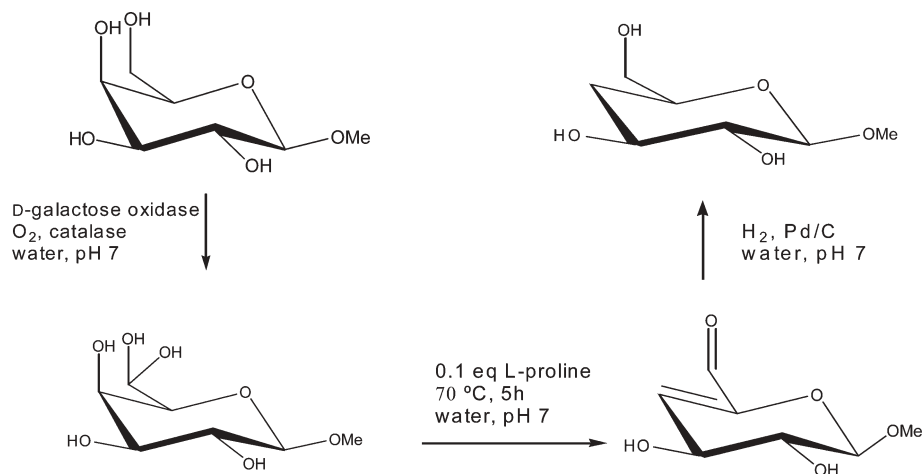


Fig. 22 One-pot, three-step synthesis of a deoxy sugar.

Catalytic cascade processes

The widespread application of chemo- and biocatalytic methodologies in the manufacture of fine chemicals is resulting in a gradual disappearance of the traditional barriers between the subdisciplines of homogeneous and heterogeneous catalysis and biocatalysis. The key to successful implementation of catalytic methodologies is integration of catalytic steps in multistep organic syntheses and downstream processing. The ultimate in integration is to combine several catalytic steps into a one-pot, multi-step catalytic cascade process.⁶³ This is truly emulating nature where metabolic pathways conducted in living cells involve an elegant orchestration of a series of biocatalytic steps into an exquisite multicatalyst cascade, without the need for separation of intermediates. Such ‘telescoping’ of multi-step syntheses into a one-pot catalytic cascade has several advantages—fewer unit operations, less solvent, and reactor volume, shorter cycle times, higher volumetric and space time yields and less waste (lower E factor)—which translates to substantial economic and environmental benefits. Furthermore, coupling of reactions together can be used to drive equilibria towards the products, thus avoiding the need for excess reagents. On the other hand, there are several problems associated with the construction of catalytic cascades: catalysts are often incompatible with each other (*e.g.* an enzyme and a metal catalyst), rates are very different and it is difficult to find optimum conditions of pH, temperature, solvent, *etc.* Catalyst recovery and recycle is complicated and downstream processing is difficult. Nature solves this problem by compartmentalisation of the various biocatalysts. Hence, compartmentalisation *via* immobilisation is conceivably a way of solving these problems in cascade processes. It is also worth noting that biocatalytic processes generally proceed under roughly the same conditions—in water at around ambient temperature and pressure—which facilitates the cascading process.

An example of a one-pot, three-step catalytic cascade is shown in Fig. 22. In the first step galactose oxidase catalyses the selective oxidation of the primary alcohol group of galactose to the corresponding hydrated aldehyde. This is followed by L-proline catalysed elimination of water and catalytic hydrogenation, affording the deoxy sugar.⁶⁴

Similarly, we recently combined an asymmetric hydrogenation with a supported chiral Rh catalyst followed by an enzymatic hydrolysis of the product into a one-pot cascade process in water as the only solvent (Fig. 23).⁶⁵

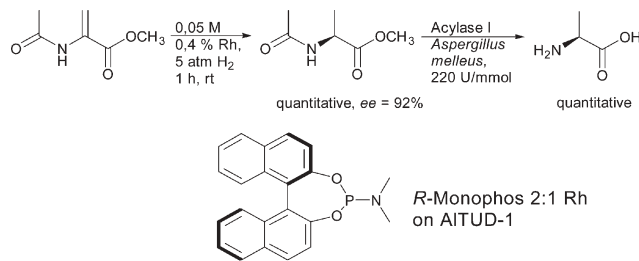


Fig. 23 Chemoenzymatic synthesis of an amino acid.

In the context of immobilisation of multiple enzymes for biocatalytic cascades the so-called Cross-Linked Enzyme Aggregates (CLEAs) are of interest.⁶⁶ They exhibit high activity retention and stability and can be readily recovered and recycled without any loss of activity. Furthermore, the method is exquisitely simple—precipitation from an aqueous buffer followed by cross-linking with, for example, glutaraldehyde—and is applicable to a broad range of enzymes. It does not require highly pure enzyme preparations and it actually constitutes a combination of purification and immobilisation into one step. The methodology can also be applied to the co-immobilisation of two or more enzymes to give ‘combi CLEAs’ which are more effective than mixtures of the individual CLEAs. These are ideally suited to conducting enzymatic cascade reactions in water, where an equilibrium can be shifted by removing the product in a consecutive biotransformation. For example, we have used a combi CLEA containing an *S*-selective nitrilase (from *Manihot esculenta*) and a nonselective nitrilase, in DIPE–water (90 : 10) at pH 5.5, 1 h, for the one-pot conversion of benzaldehyde to *S*-mandelic acid (Fig. 24) in high yield and enantioselectivity.⁶⁷

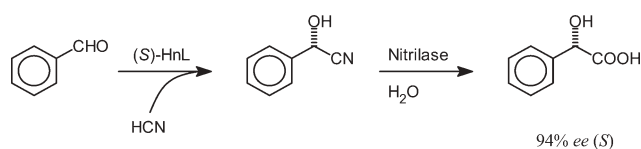


Fig. 24 One-pot conversion of benzaldehyde to *S*-mandelic acid with a combi CLEA.

Conclusions and prospects

The employment of catalytic methodologies—homogeneous, heterogeneous and enzymatic—in nonconventional reaction media holds much promise for the development of a sustainable chemical manufacturing industry. Water, for example, is cheap, abundantly available, nontoxic and nonflammable and the use of aqueous biphasic catalysis provides an ideal basis for recovery and recycling of the (water-soluble) catalyst. Water is also the ideal solvent for many processes catalysed by nature’s catalysts, enzymes. Hence, the use of water as a reaction medium meshes well with the current trend towards a sustainable chemical industry based on the utilisation of renewable raw materials rather than fossil fuels as the basic feedstock.

Supercritical carbon dioxide also has many potential benefits in the context of sustainability. In common with water, it is cheap, abundantly available, nontoxic and nonflammable. It is also an eminently suitable solvent for homogeneous, heterogeneous and biocatalytic processes and is readily separated from the catalyst and products by simple release of pressure. Reaction rates are very high in scCO₂, owing to its intermediate properties, between a gas and a liquid. Biphasic systems involving scCO₂ with, for example an ionic liquid or polyethylene glycol, also hold promise as reaction media for a variety of catalytic processes integrated with product separation and catalyst recycling.

Fluorous biphasic systems and ionic liquids are potentially attractive alternatives for performing conversions which are not feasible in water or supercritical carbon dioxide. Both types of solvent suffer from the (perceived or real) disadvantages of high price and/or limited availability coupled with issues of biodegradability and/or aquatic toxicity. They undoubtedly have commercial potential in niche applications.

The ultimate in sustainable catalytic processes is the integration of chemocatalytic and/or biocatalytic steps into catalytic cascade processes that emulate the metabolic pathways of the cell factory. One-pot syntheses *via* catalytic cascade processes, involving chemo- and biocatalysis, and based on water and carbon dioxide as basic raw materials and reaction media, would seem to provide the ideal basis for a sustainable chemical industry.

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